REVIEW ARTICLE

Redefining resection margin status in pancreatic cancer

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Abstract

Curative resection is crucial to survival in pancreatic cancer; however, despite optimization and standardization of surgical procedures, this is not always achieved. This review highlights that the rates of microscopic margin involvement (R1) vary markedly between studies and, although resection margin status is believed to be a key prognostic factor, the rates of margin involvement and local tumour recurrence or overall survival of pancreatic cancer patients are often incongruent. Recent studies indicate that the discrepancy between margin status and clinical outcome is caused by frequent underreporting of microscopic margin involvement. Lack of standardization of pathological examination, confusing nomenclature and controversy regarding the definition of microscopic margin involvement have resulted in the wide variation of reported R1 rates that precludes meaningful comparison of data and clinico-pathological correlation.

Keywords

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Introduction

The prognosis for patients with ductal adenocarcinoma of the pancreas is poor.[1] As the response of this cancer to chemo- and radiotherapy is limited, surgical resection is currently the only potentially curative treatment. Only 10–20% of pancreatic cancer patients can undergo surgical resection, and within this patient group, resection margin (RM) involvement has been established as a key prognostic factor.[2–6]

The rate of microscopic RM involvement (R1) reported in the literature varies markedly, from below 20% to over 75%.[7–17] A recent meta-analysis highlighted that even in randomized controlled trials, in which a higher than average level of standardization may be expected, the R1 rate ranged from 0% to 83%, limiting the scope for meaningful comparison and precluding conclusions regarding the prognostic significance of RM status.[18]

Because RM involvement is generally believed to be determined by the quality of surgery, a low R1 rate is often seen as an indicator of high-quality surgery. Recent studies, however, have brought the pathologist as a second player into the field, based on the growing awareness that standardization and meticulousness of the pathological examination have a significant impact on the accuracy of the reported RM status.[16,19,20] The R1 rate is therefore a performance measure not only for the surgeon, but possibly also for the reporting pathologist.

Recent scrutiny of the pathological examination of pancreatoduodenectomy (PD) specimens further revealed a stark lack of consensus regarding terminology and definitions that are key to the reporting of the RM status.[21,22] With this additional set of confounding factors, concern is growing that pathological reporting may be inconsistent and hence bias prediction of outcome, skew epidemiological data and hamper progress in our understanding of the natural history of pancreatic cancer.

The recent development in the pathological assessment of RMs in pancreatic cancer and the ensuing implications for patient management are reviewed and discussed in the context of advances in pancreatic surgery.

Surgical technique and margin involvement

Surgeons over the years have pushed the boundaries of surgical resection for the limited group of patients with resectable disease in an attempt to achieve complete tumour clearance with negative margins.

The traditional Kausch–Whipple procedure (PD) evolved in the early 1990s to the pylorus-preserving Kausch–Whipple variant [pylorus-preserving pancreatoduodenectomy (PPPD)] with initially varied outcomes reported using the two techniques in large case series.[23–25] A recent Cochrane Database Systematic Review[26] and three prospective randomized trials compared the two techniques[27–29] and concluded that there were no long-term survival differences between the two groups. It is difficult to draw meaningful conclusions regarding the RM status after PD and PPPD, as these data are not available for all studies. However, a detailed account of the RM status was presented in a Dutch study, which did not observe a significant difference in R1 rate (PD: 17%, PPPD: 26%, $P = 0.23$), or indeed in long-term patient survival.[29] Interestingly, an international workshop on surgical procedures in pancreatic cancer recommended that the pylorus-preserving operation should not be used for carcinomas located in the antero-superior part of the pancreatic head.[30]

The same workshop defined the extent of dissection that should be performed as part of a standard (PP-)PD and a procedure with extended lymphadenectomy. Although the latter was proposed to achieve a radical curative resection for pancreatic cancer by careful removal of retroperitoneal lymph nodes and soft tissues, the Johns Hopkins group found no significant difference in resection margin status between standard and radical PD (12% vs. 7%; $P = 0.11$).[31] Unfortunately, very limited data are available on margin status after radical surgery, and in particular no information has been published on the margins of the extended resection areas. As randomized trials[31–33] failed to show any survival advantage after extended lymphadenectomy, current recommendation is for only a standard lymphadenectomy in conjunction with a PD or PPPD.[34]

Pancreatic cancers involving the portal vein and/or superior mesenteric vein can be resected safely either by a lateral sleeve resection or a segmental resection with or without the use of an interposition graft. Recent analysis of a large series convincingly showed that survival of patients after vascular resection is similar to that of patients in whom vascular resection is not required.[35] Less clear, however, is the impact of vascular resection on margin involvement. While some studies report a higher incidence of RM involvement after vascular resection,[17] others observe no difference in R1 rate between PD with or without vascular resection.[35] These conflicting observations are difficult to reconcile, but comparison of the R1 rate for pancreatic resection without vascular resection in these studies suggests that – as outlined below – differences in the pathological assessment of the RMs may have clouded the picture.

Histopathological assessment and margin involvement

Recent studies from European and UK centres have highlighted the impact of histopathological examination on the R1 rate.[16,19] After introduction of a rigorous standardized pathology protocol, both groups observed a significant increase in the R1 rate for pancreatic cancer, from 53% to 85%[16] and 14% to 76%.[19] A follow-up study by the UK group confirmed the consistency of this high R1 rate and thus the robustness of margin assessment if a detailed standardized protocol is consequently used.[20] The observations of these studies indicate that resection margin involvement is a common finding in pancreatic cancer, which risks being under-recognized if pathological examination is not thorough.

The histopathological diagnostic process encompasses multiple steps, including specimen dissection, tissue sampling, microscopic examination, and reporting of findings. As discussed below, each step is fraught with a lack of consensus and standardization, and therefore open to different approaches and interpretations that potentially result in inconsistent reporting of the margin status. Opinions even differ on what exactly constitutes the resection margin in PD specimens, and hence, which parts of the specimen should be included in the pathological examination.

Circumferential resection margins in PD specimens

While evaluation of the transection margins of the pancreatic neck, common bile duct, stomach and/or duodenum is a well-established part of routine practice, much confusion exists regarding the circumferential resection margin (CRM), which is in part a result of differences in terminology.

As illustrated in Fig. 1, it seems sensible to distinguish between the anterior and posterior surfaces of the pancreatic head, which are separated by the medial CRM. The latter faces the superior mesenteric vein (SMV) and has a shallow groove-like shape and a fairly smooth surface. Flanking the medial (or SMV) CRM to the left is a relatively small area of rougher texture that faces the superior mesenteric artery (SMA) and joins by an acute angle the slightly fibrous but smooth posterior surface of the pancreatic head, which overlies the aortocaval groove. The posterior CRM is often referred to as the retroperitoneal margin – a misnomer as the entire pancreas is located in the retroperitoneum – and sometimes includes the SMA margin.[16,17,36] The medial, groove and SMV margins are used more or less synonymously, whereas the uncinate process margin and the vascular margin usually refer to the SMA margin.[17,22,37]

Controversy exists over the anterior surface of PD specimens as to whether it should be regarded as part of the CRM. While it is an anatomical surface, not a true RM, presence of tumour cells at the anterior surface is likely to increase the risk of local recurrence. This surface is therefore included in the assessment of the CRM in some European centres[16,19,38] and an integral part of the Japan Pancreas Society (JPS) classification,[39] but usually left unconsidered by pathologists in the USA according to the AJCC recommendations.[40] Limitation of the assessment to the SMA or 'uncinate' margin may at least partially explain the lower R1 rates observed in some high-volume US pancreatic cancer centres.[17]

Although microscopic margin involvement is staged as 'R1' irrespective of which parts of the CRM are involved, detailed CRM
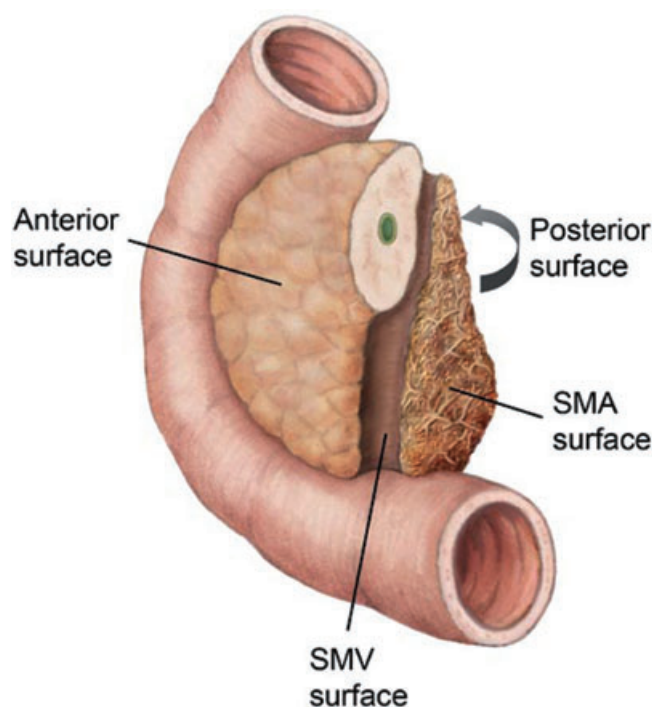
Figure 1 The circumferential resection margin in pancreatoduodenectomy (PD) specimens consists of the anterior surface, the medial surface facing the superior mesenteric vein (SMV), the surface flanking the superior mesenteric artery (SMA) and the posterior surface

Figure 2 Slicing of pancreatoduodenectomy (PD) specimens in an axial plane provides good views of the tumour and its relationship to the key anatomical structures and the entire circumferential resection margin

mapping is important, first and foremost to allow for feedback to the surgical team. In addition, through accurate correlation with multimodality imaging, CRM mapping could facilitate improved pre-operative assessment of resectability and identification of areas at risk of incomplete resection. Finally, data from margin mapping are required to reveal the significance of involvement of each individual CRM in terms of survival.

Dissection of PD specimens

Existing literature on the pathological examination of PD specimens – national guidelines, standard textbooks and published single or multicentre studies[38,41–45] – reveals that a wide range of dissection techniques are currently used, many of which follow tradition rather than evidence-based rationale. While significant progress has been made through refinement and standardization of technical procedures in surgery and pre-operative imaging of pancreatic cancer, histopathology has failed to follow suit.

A recent overview and comparison of the different dissection techniques[21] highlights the advantages of the so-called axial slicing technique, which has been used increasingly in European and UK pancreatic cancer centres. As illustrated in Fig. 2, the technique is based solely on serial slicing of the pancreatic head in an axial plane, i.e. perpendicular to the longitudinal axis of the duodenum. It does *not* prescribe longitudinal opening of the pancreatic or bile
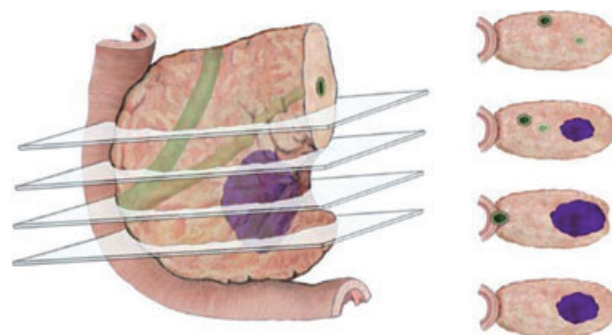
duct, hence the entire surface (or CRM) of the pancreatic head remains intact. Axial slicing is easy to perform, independent of the location and nature of the pathology encountered, and allows extensive views of the lesion and its relationship to key anatomical structures. Interestingly, axial slicing was the standardized dissection technique used in the recent studies that reported an unusually high R1 rate of over 75%.[16,19,20] The frequent identification of margin involvement reported in these studies is at least partially explained by the fact that all parts of the CRM can be inspected in each specimen slice obtained with this technique.

Although beyond the scope of this review, it is worth mentioning that by using the axial slicing technique, a high lymph node yield[19,20] well above the currently recommended minimum of 15 lymph nodes[46,47] can be achieved. Furthermore, if axial slicing is performed in combination with photodocumentation of the specimen slices, macroscopic findings can be reviewed in great detail at any time. This is helpful for the reporting pathologist, during multidisciplinary case discussion, and, not less importantly, for pathology review in multicentre trial work. As identification of the cancer origin – pancreatic, ampullary or distal bile duct – is based mainly on gross findings, photographs of specimen slices would allow pathology review to extend beyond the mere microscopic re-assessment of the exact tumour type.

Tissue sampling

Unlike other digestive tract cancers in which the invasive tumour front is usually well-defined and reliably identifiable by gross inspection, the boundaries of pancreatic and distal bile duct cancers are often obscured by fibrosis and inflammatory changes associated with tumour-induced obstructive pancreatitis. The highly dispersed, discontinuous growth that is characteristic of pancreatobiliary cancer further contributes to the difficulty of identifying the tumour periphery. With naked-eye inspection being unreliable in this respect, extensive sampling of the tumour and nearest CRMs is essential. Failure to do so will inevitably lead to underestimation of margin involvement, as the R1 rate corre-

lates directly with the extent of tissue sampling.[16] The importance of extensive sampling is further supported by a recent molecular study based on K-ras analysis, which detected cancer cells in the margins of 53% of PD specimens deemed to be margin-negative by histological assessment.[48]

Intra-operative frozen section examination

In many centres, intra-operative frozen section examination is regularly used to assess possible tumour involvement of the transection margin of the pancreatic neck or common bile duct. In contrast, samples from the CRMs are usually not submitted for intra-operative frozen section. The surgical technique for a standard PD resection involves clearance of all tissues along the portal vein/SMV and along the right of the SMA, and therefore these margins cannot be improved by the surgeon, even if they were found to be involved using tumour on frozen section analysis. Recently, protocols for the intra-operative frozen section examination of the SMA or 'uncinate' margin have been proposed[37,49] with the intention to guide the surgeon in the extent of resection around the SMA. However, during a standard PD, any attempt to resect tissue close to or on the uncinate margin would be by definition an incomplete resection and runs the risk of a discontinuous resection and creating a positive margin should the tumour involve the uncinate process. By following the standard technique for PD the need for intra-operative frozen section analysis of this margin should be obviated.

Definition of R1: 1 mm clearance?

One further important reason for the remarkable variety in reported R1 rates is the lack of consensus regarding the definition of microscopic margin involvement. In the USA, pathologists will report a margin as positive only if tumour cells are present *at the* surface, i.e. if the clearance equals 0 mm.[17,45,49] In contrast, many pathologists in Europe and the UK use a definition based on a 1 mm clearance.[38] The latter '1 mm rule' is a mere adoption of the definition of R1 in rectal cancer, which is based on meticulous correlation between measured minimum clearance and local tumour recurrence.[50,51] Such a clinicopathological correlational study has not been performed for pancreatic cancer, mainly because, for the want of management implications, detailed diagnostics are usually not performed in patients presenting with signs of tumour recurrence.

In the absence of data linking local recurrence rate to minimum tumour clearance, resort has to be taken to a different approach. The distance of minimum clearance is obviously determined by the growth pattern of a particular cancer. Absence of tumour cells at or within 1 mm to the specimen surface is less likely to indicate complete resection, i.e. absence of tumour beyond the line of resection, if the tumour growth pattern is dispersed rather than compact. A recent study analysing the growth patterns of rectal cancer and ductal adenocarcinoma of the pancreas revealed a significantly more dispersed growth pattern of the latter, in particular in the periphery of the tumour, close to the invasive front.[52]

Hence, an R1 definition based on a 1 mm clearance that is adequate for compact-growing rectal cancer, is likely to underestimate microscopic margin involvement in pancreatic cancer.

The above considerations apply to the assessment of tumour involvement of true margins, either transection margins or CRMs. As the anterior surface of the pancreatic head is an anatomical surface rather than a surgical margin, it seems sensible to apply the 0 mm clearance rule for the assessment of the anterior surface.

Mode of tumour propagation at the margin – does it matter?

A further point of controversy regarding microscopic margin assessment pertains to the mode of tumour propagation: should tumour cells inside lymphovascular channels, perineural clefts or lymph nodes within 1 mm to the RM also be reported as R1? The difficulty in answering this question is twofold. First, tumour cells within lymphovascular channels and perineural clefts are in transit and have a mode of spread that differs from that of cancer cells infiltrating tissue planes. Hence, the above considerations regarding growth pattern and minimum clearance do not apply.

The second difficulty is of a conceptual nature. Lymphovascular or perineural tumour propagation indicates a risk of *regional* tumour spread. Curative resection is commonly understood as successful *local* clearance of a tumour, acknowledging that locoregional tumour recurrence as a result of lymph node metastasis or spread along peripheral nerves cannot be prevented by an R0 resection.

While the confusion regarding margin involvement and lymphovascular or perineural tumour propagation seems to be primarily one of concepts and terminology, the question of positive lymph nodes close to the RM can be addressed by considerations based on tumour growth pattern. Tumour cells inside a lymph node tend to grow within the confines of the well-defined lymph node capsule, and hence the 0-mm clearance approach seems to be appropriate. Ultimately, however, tumour cells may breach the lymph node capsule and infiltrate the surrounding soft tissue, at which stage the R1 definition based on tumour growth pattern (currently, by default, 1 mm clearance) becomes applicable.

R1 rate and clinical outcome

Although resection margin involvement is an established prognostic factor, the overall survival figures in series with low R1 rates do not differ significantly from those with higher R1 rates. Interestingly, as illustrated in Table 1, the best outcome after curative resection is observed in two studies with the by far highest R1 rate.[16,20] In contrast, none of the other listed studies show a correlation between R1 rate and median survival or survival benefit of curative resection. As expected, the survival figures for noncurative resections are similar in all studies, indicating a comparable level of care along the patient pathway.

Table 1 Survival data following curative and non-curative surgical resection for pancreatic cancer

Reference (First author/year)	No of patients	RM status	R1 rate (%)	Median survival R1/R2 (months)	Median survival R0 R0 (months)
Menon (2009)[20]	27	R1	82	14	>55
Westgaard (2008)[36]	40	R1	45	11	16
Raut (2007)[17]	360	R1	17	22	28
Verbeke (2006)[16]	26	R1	85	11	37
Neoptolemos (2001)[5]	541	R1	19	11	17
Benassai (2000)[13]	75	R1, R2	20	9	17
Sohn (2000)[14]	616	R1	30	12	19
Millikan (1999)[12]	84	R1	29	8	17
Nishimura (1997)[11]	157	R1, R2	45	6	12
Sperti (1996)[10]	113	R1, R2	17	7	14
Nitecki (1995)[9]	174	R2	16	9	NA
Yeo (1995)[8]	201	R1, R2	29	10	18
Willett (1993)[7]	72	R1	51	12	20

R0: clear margins; R1: microscopic margin involvement, R2: gross margin involvement.

Both studies with a high R1 rate for pancreatic cancer differ from the other studies by the fact that pathological examination was performed according to a rigorous, fully standardized examination protocol, including axial specimen slicing, photodocumentation and extensive tissue sampling. Although both studies are based on small series, and hence confirmation on larger case numbers is required, their results seem to indicate that meticulous pathological assessment allows accurate identification of RM involvement, and consequently, reliable prognostic stratification. In contrast, if pathological assessment underestimates RM involvement, incorrect reporting of R0 resection obfuscates the difference in outcome between the R0 and R1 subgroups.

The rate of local tumour recurrence is an alternative outcome measure with which the R1 rate can be compared. Studies based on imaging or post-mortem findings typically report a local recurrence rate for pancreatic cancer of 75–85%.[53–55] This seems to be at odds with the R1 rate, which in the majority of published series lies well below 30–40%. Interestingly, the local recurrence rate is significantly lower in ampullary cancer (approximately 28%) than in distal bile duct cancer (58–74%),[56–59] and in some studies this corresponds with differences in R1 rate for those cancers.[16,20,36] Hence, incorrect diagnosis of the tumour origin may lead to inclusion of ampullary or distal bile duct adenocarcinomas in pancreatic cancer series and result in a misleadingly low R1 rate.

Despite the current lack of consensus in terminology to denote the different CRMs, most studies seem to agree that the posterior and medial CRMs are affected most frequently.[16,19,20,59,60] However, the prognostic significance of tumour involvement of each individual CRM is currently not known. While data on detailed CRM mapping are too scarce to allow any conclusions, occasional single-centre studies suggest prognostic relevance of particular CRMs in pancreatic[61,62] and distal bile duct cancer.[63]

The way forward

As histopathology remains the cornerstone for stratification of pancreatic cancer patients who underwent surgical resection, consensus regarding the definition of microscopic margin involvement and standardization of the examination protocol are important first steps towards improved patient management. Although standardization is essential to increase consistency and completeness of histopathology reporting, it does not ensure diagnostic accuracy. The latter can be achieved only by continuous quality assessment of pancreatic pathology reporting and comparison against benchmarks that need to be developed once standardization has been widely implemented and allowed generation of consistent data. Once standardization and quality monitoring of pathology are in place, trials to assess novel treatment strategies can be rolled out to multiple national and international centres without the risk of being biased by inconsistent pathological data.

Through careful correlation with imaging, accurate pathological assessment of the margins could be used to refine pre-operative prediction of margin involvement, as it is done for rectal cancer, and assess the impact of pre-operative treatment on resection margin status.

Novel surgical techniques such as the 'No touch isolation technique' have been developed to reduce cancer cell dissemination by avoidance of intra-operative tumour manipulation. While the results in terms of tumour recurrence have yet to be proven, this technique would have little bearing on resection margins, in particular if the principles of a standard (PP-)PD are adhered to.[64]

Conclusions

The currently recommended surgical treatment for pancreatic cancer is a PD, classic or pylorus-preserving, with a standard

lymphadenectomy and, in case of vascular involvement, mesenterico-portal vein resection.

While it is acknowledged that these surgical procedures do not always result in curative resection, published data on the incidence of margin involvement vary widely between studies and do not convincingly correlate with patient outcome.

Recent studies indicate that if pathological assessment is detailed and standardized, margin involvement is found in >75% of PD specimens for pancreatic cancer. These observations are not without important clinical implication. If indeed the majority of surgical resections are non-curative, then adjuvant treatment needs to be offered to a much larger patient group.

The reasons for underestimation of margin involvement are manifold and include, amongst others, controversy regarding the definition of microscopic margin involvement and the lack of a detailed, standardized pathology examination protocol. Not only the management of individual patients, but also the success of multicentre trials to assess novel treatment strategies will to a large extent depend on the resolution of these issues. Without robust and reliable pathological data, trials are unlikely to produce compelling evidence.

Conflicts of interest

None declared.

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